blood advances

POINT Imatinib is still recommended for frontline therapy for CML

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This article has a companion Counterpoint by Cortes.

Introduction

The treatment of chronic phase chronic myeloid leukemia (CP-CML) was revolutionized by the introduction of tyrosine kinase inhibitors (TKIs) against the chimeric fusion protein BCR-ABL1. The introduction of imatinib, the first *BCR-ABL1* TKI, changed a usually fatal disease with long-term survival of <15%[1] into a manageable chronic condition for the vast majority of patients. After imatinib was approved for treating CP-CML, efforts to improve efficacy led to frontline approvals of 3 second-generation agents: nilotinib, dasatinib, and bosutinib. These agents have increased potency against BCR-ABL1, and they produce cytogenetic and molecular remissions more rapidly than imatinib; however, this has not yet translated into better long-term outcomes.[2] When evaluating therapeutic options for newly diagnosed patients with CP-CML, one must consider clinically relevant end points such as progression-free survival (PFS) and overall survival (OS) as well as tolerance, safety, cost, and possible discontinuation.[3] Here, we review these end points to demonstrate that imatinib should still be recommended as frontline therapy for most adults with low- and intermediate-risk CP-CML.

Efficacy

Data from the IRIS trial and CML Study IV, each with more than 10 years of follow-up, established long-term efficacy for imatinib that has yet to be replicated by newer agents.[4,5] In the IRIS trial, imatinib 400 mg daily demonstrated improved effectiveness and tolerance over the previous standard of interferon and cytarabine.[4] Complete cytogenetic remissions (CCyRs) were significantly higher with imatinib after 18 months (76% vs 15%; $P < .001$). After a median follow-up of 10.9 years, the OS of patients treated with imatinib was 83.3%; only 15.9% and 6.9% of patients discontinued treatment as a result of unsatisfactory therapeutic effect or adverse events (AEs), respectively. In CML Study IV,[5] newly diagnosed patients received imatinib 400 mg daily, 800 mg daily, or 400 mg daily plus either interferon or cytarabine. At 10 years, combined OS was 84%; 89% achieved major molecular remission (MMR) defined as *BCR-ABL1* transcript level ≤0.1%, and 72% achieved $MR^{4.5}$ defined as a 4.5-log reduction in *BCR-ABL1* transcripts from a standardized baseline. With a median follow-up of 7.1 years, 64% of patients remained on imatinib, and 22% had switched to a second-generation TKI.

The ENESTnd, DASISION, and BFORE trials were the primary registration trials for the frontline approvals of nilotinib, dasatinib, and bosutinib, respectively. These trials compared the efficacy of imatinib 400 mg daily with their corresponding second-generation TKIs and used molecular end points as primary outcomes. Assessing the results by disease risk score (eg, Sokal, Hasford, or EUTOS) and clinically relevant end points demonstrated that imatinib remains a valid frontline option for low- and intermediate-risk patients.[2,6-10]

In the ENESTnd trial, patients were randomly assigned to nilotinib 300 mg or 400 mg twice daily or to imatinib.[11] The primary outcome of MMR at 12 months was significantly higher for nilotinib (44% [300 mg] and 43% [400 mg]) than for imatinib (22%). The DASISION trial randomly assigned patients to receive either dasatinib 100 mg or imatinib 400 mg daily.[12] Significant improvement in the primary end point of CCyR at 12 months was observed for patients receiving dasatinib vs imatinib (77% vs 66%).

Five-year efficacy data for the DASISION and ENESTnd trials are presented in Table 1.[13,14] Despite the differences in molecular outcomes, there were no differences in PFS and OS between imatinib and each second-generation TKI. In ENESTnd, differences in PFS and OS for Sokal low- or intermediate-risk patients were insignificant between imatinib and nilotinib (Table 2). Twice as many patients had

Table 1. Efficacy end points for the DASISION and ENESTnd trials

	DASISION[13]		ENESTnd[14]		
	Imatinib	Dasatinib	Imatinib	Nilotinib	
	400 mg daily (n = 260)	100 mg daily (n = 259)	400 mg daily (n = 283)	300 mg twice daily (n = 282)	400 mg twice daily (n = 281)
Cumulative MMR at 5 y, %	64	76	60	77	77
$MR^{4.5}$ at 5 y, %	33	42	31	54	52
Progression to AP/BC, %	7	5	7	4	3
5-y OS (ITT), %	90	91	92	94	96
5-y PFS, %	86	85	91	92	96

AP, accelerated phase; BC, blast crisis; ITT, intention to treat.

detectable mutations emerge while they were receiving imatinib (8.9%) compared with patients who received nilotinib 300 mg (4.8%) or 400 mg (5.1%). However, the majority of these mutations occurred in patients with intermediate or high Sokal scores, and 67% of mutations in patients who were receiving imatinib remained sensitive to nilotinib.[15] Notably, a second randomized trial of nilotinib that enrolled 267 Chinese patients[16] did not show differences in rates of confirmed CCyRs (84% vs 87%) or freedom from progression (95% each) at 24 months.

The BFORE trial[17] compared the dual *SRC*/*ABL1* TKI bosutinib 400 mg daily with imatinib. The previous bosutinib trial (BELA[18]) did not meet its primary end point of difference in 12-month CCyR rates (bosutinib CCyR of 70% vs imatinib CCyR of 68%; $P = .6$) but did show improvements in MMR. The BFORE trial was therefore designed with 12-month MMR as the primary end point and was positive: 47.2% vs 36.9% in favor of bosutinib ($P = .02$). However, estimated 12-month OS was similar (99.6% for patients receiving bosutinib and 97.9% for patients receiving imatinib).

Although early surrogate end points such as CCyR, MMR, and early molecular response (EMR, defined as a transcript level $<10\%$ at 3 months) were emphasized in registration trials, long-term follow-up has not yet translated into improved PFS or OS. A recent meta-analysis of next-generation TKIs did not show differences in these measures when compared with imatinib.[19] Survival is arguably most important to the patient, and these data remain as robust for imatinib as for other agents.

Recent studies have assessed the ability of CML patients in a sustained deep molecular remission to discontinue TKI therapy. Prospective trials that discontinue imatinib or second-generation TKIs have shown similar rates of treatment-free remission (TFR): ~50% at 24 months.[20,21] Although more patients treated with second-generation TKIs attain deep molecular remission, other factors such as initial Sokal low-risk score, for which outcomes on imatinib are similar, as well as depth and duration of prior remission appear to be predictive for TFR and may negate any perceived differences.[22]

Tolerance and safety

Our recommendation is also based on the long-term safety data, adherence, and lesser toxicity of imatinib compared with those of second-generation agents. Eight-year safety data from the CML Study IV[23] reported AEs in 76% of all patients receiving imatinib, of which only 22% were grade 3 or 4. Most AEs were mild and manageable. Importantly, no new, late toxicity has been observed either on this study, on the IRIS trial, or after nearly 20 years of use.

The second-generation TKIs have demonstrated more early and late toxicities than imatinib. AE results from the ENESTnd, DASISION, and BFORE trials are presented in Table 3 and show greater rates of grade 3 to 4 AEs, serious AEs, and/or AEs leading to discontinuation for these agents. Significantly increased nonhematologic toxicities of the second-generation TKIs are presented in Table 4. Major bleeding was seen in 6% of patients receiving dasatinib and was thought to be the result of an inducible platelet dysfunction. Treating patients with dasatinib while they are thrombocytopenic ($<75 \times 10^9$ platelets per liter) or while they are receiving antiplatelet agents should be performed with caution.

Vascular occlusive events (VOEs) are particularly prevalent among older patients and those with cardiovascular risk factors.

Table 2. Outcomes for Sokal low- and intermediate-risk patients on the ENESTnd trial

ENESTnd outcomes for Sokal low- and intermediate-risk patients	Imatinib	Nilotinib	
	400 mg daily (n = 283)	300 mg twice daily (n = 282)	400 mg twice daily (n = 281)
Low-risk PFS, %	100	96	99
Low-risk OS, %	100	97	99
Intermediate-risk PFS, %	88	93	97
Intermediate-risk OS, %	89	94	97

There were no significant differences between any groups. Data from Saglio et al[11] and Hochhaus et al.[14,15]

Table 3. Overall toxicities reported on randomized clinical trials

	ENESTnd		DASISION		BFORE	
Toxicity	Imatinib 400 mg daily	Nilotinib 400 mg twice daily	Imatinib 400 mg daily	Dasatinib 100 mg daily	Imatinib 400 mg daily	Bosutinib 400 mg daily
Grade 3 to 4 AE, %	59	72	NR	NR	43	56
Serious AE, %	25	33	NR	NR	NR	NR
AE leading to discontinuation, %	14	20	7	16	11	14

NR, not reported.

Patients treated with imatinib have been associated with lower rates of VOEs when compared with patients not treated with TKIs, suggesting a cardioprotective effect. A meta-analysis of more than 3000 patients[24] confirmed significantly increased VOEs with dasatinib (odds ratio [OR], 3.86) and nilotinib (OR, 3.45) compared with imatinib. The differences observed with bosutinib (OR, 2.77) were not significant. In addition, the exclusion criteria used for the ENESTnd and DASISION trials were based on their respective second-generation TKI toxicity spectrum and were broader than the exclusions necessary for imatinib alone. A report on 207 patients from an unselected CP-CML population found that 22.7% and 17.4% would not have been eligible for the ENESTnd or DASISION trials, respectively, because of additional excluded comorbidities.[25] These patients went on to have significantly higher rates of nonhematologic toxicity than those who met eligibility criteria.

Cost

Another consideration when deciding on appropriate therapy is affordability, especially when treatment may continue throughout life. Higher out-of-pocket expenses have been linked to lower quality-of-life scores,[26] delayed TKI initiation,[27] and decreased adherence.[28] TKI adherence of less than 90% is associated with decreased rates of MMR.[29] In 2016, imatinib became the only *BCR-ABL* TKI to come off patent. Generic formulations for imatinib are less expensive than the branded formulation (Gleevec) and much less expensive than second-generation agents.[30] Although all TKIs remain expensive for patients and the health care system, cost-effectiveness analyses continue to show benefit for imatinib-first sequential strategies over the initial use of second-generation agents.[31-33] When recommending generic imatinib, clinicians must ensure that the supply is from an approved source because there are counterfeit formulations that are not bioequivalents.[34]

Our current approach

Once CML is suspected, we establish a diagnosis through a peripheral blood qualitative polymerase chain reaction (PCR) assay or fluorescent in situ hybridization for *BCR-ABL1*, and we perform a bone marrow examination to assess morphologic stage and obtain metaphase cytogenetics. A PCR assay is required to identify rare molecular variants of *BCR-ABL1* that cannot be detected by standard primers and thus are not amenable to molecular monitoring. We take into account the patient's history, including performance status, comorbidities, cardiovascular risk factors, current medications, and insurance status. Physical examination should include blood pressure and spleen size assessments. Additional testing includes a complete blood count with white blood cell differential, a comprehensive metabolic panel, lactate dehydrogenase level, and a baseline electrocardiogram to measure the QT interval, which leads to calculation of the Sokal risk score.

For patients with a low- to intermediate-risk Sokal score, we begin imatinib 400 mg daily.[3] During the first month of treatment, we see patients once per week to assess toxicity and blood counts. Most patients will achieve hematologic remission within 1 to 2 months. We use transfusions and/or filgrastim to maintain adequate blood counts instead of interrupting imatinib for cytopenias. For the 20% of patients presenting with a high Sokal score, we prefer to start treatment with either dasatinib or nilotinib. The choice between these agents is made mostly by their AE profiles and patient preferences. We avoid dasatinib for those with lung disease or gastrointestinal bleeding and nilotinib for those with poorly controlled diabetes, hepatic disease, or cardiovascular risk factors. In the absence of these risks, the choice between these drugs then depends on preference and cost. We measure the *BCR-ABL1* transcript level in the blood after 3 months of therapy and continue the initial treatment for those with an EMR. For those

Table 4. Important idiosyncratic AEs

AE	Imatinib 400 mg daily*	Nilotinib 400 mg twice daily	Dasatinib 100 mg daily	Bosutinib 400 mg daily
Range of vascular events, %	1.1-2.5	15.9	4.7	1.5
Range of pleural effusions, %	0.8-1.9	0.7	28.0	1.5
Pulmonary hypertension, %	0.4	0.7	5.0	NR
Range of grade 3 to 4 diarrhea, %	<0.1-3.6	2.5	NR	7.8
Range of grade 3 to 4 abnormal liver function tests, %	2.9-4.2	18.5	NR	24.3

*Frequencies differ slightly by trial.

who are slow to respond or intolerant of imatinib, we consider switching to a different TKI, provided that the patients have been adherent.

Authorship

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